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The Simultaneous Double Diels-Alder Addition of 1,1-Bis(3,5-dimethylfur-2-yl)ethane; Toward a New, Asymmetric Synthesis of Long-chain Polypropionate Fragments and Analogues.

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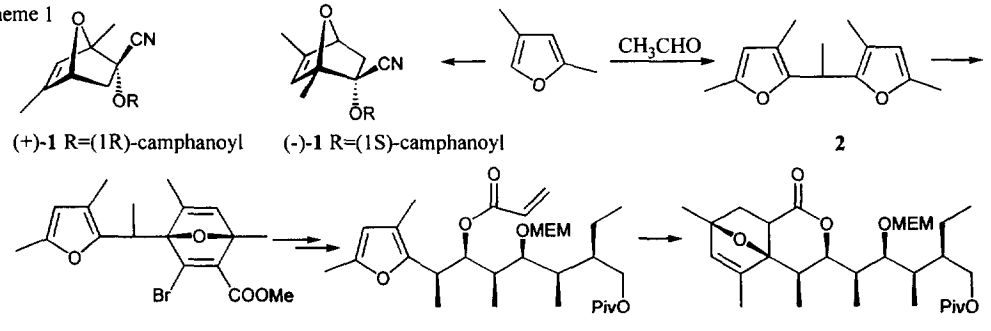
Abstract: The double cycloaddition of 1,1-bis(3,5-dimethylfur-2-yl)ethane to diethyl (E,E)-4--oxohepta-2,5-diene-1,7-dioate gave a single bis-adduct, the hydroboration of which with $IpcBH_2$ allows the creation of optically active polycyclic systems that are potential precursors of long-chain polypropionate fragments. Copyright © 1996 Published by Elsevier Science Ltd

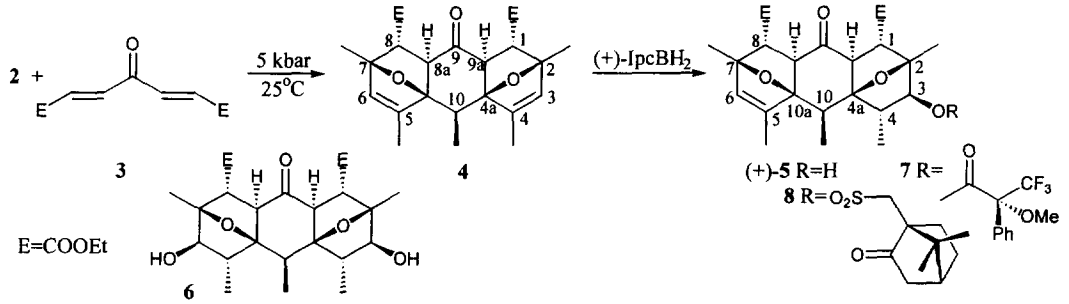
Nature provides us with a number of products of biological interest containing long-chain polypropionate fragments.[1,2] Because of their rarity, total synthesis can, in principle, supply sufficient quantities for their pharmaceutical testing, and very importantly, for obtaining non-natural analogues. Among the synthetic methods available[1,3] the simultaneous two-directional chain elongation followed by kinetic or chiral desymmetrization is a quite appealing approach.[4,5] We have shown[3b] that optically pure Diels-Alder adducts of 2,4-dimethylfuran such as (+)-**1** and (-)-**1** ("naked sugars of the second generation") can be used to construct long-chain polypropionate fragments containing up to eleven contiguous stereogenic centers and tertiary alcoholic moieties.[2] More recently, we demonstrated[6] that 1,1-bis(3,5-dimethylfur-2-yl)ethane, a compound obtained in one step by condensation of 2,4-dimethylfuran with acetaldehyde, can be converted into a variety of racemic polypropionate fragments with high stereoselectivity through a sequence of reactions implying two non-simultaneous Diels-Alder additions (Scheme 1). We report here that **2** can undergo two simultaneous Diels-Alder additions with a bis-dienophile such as diethyl (E,E)-4-oxohepta-2,5-diene-1,7-dioate (**3**), a compound obtained readily from diethyl 4-oxopimelate through double bromination and double HBr elimination.[7]

Scheme 1



(+)-**1** R=(1R)-camphanoyl (-)-**1** R=(1S)-camphanoyl **2**

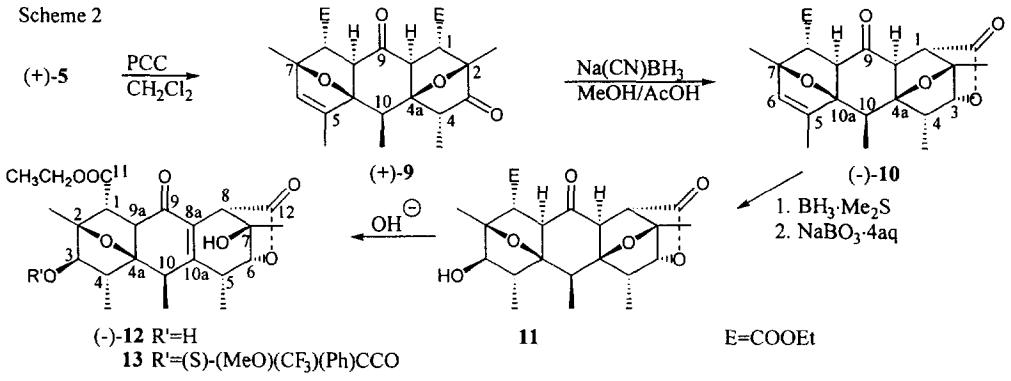
When an equimolar mixture of **2** and **3** (25% in $CHCl_3$) was pressurized for 5 hours at 5 kbar (25°C), adduct **4** was obtained in 95% yield. Its structure was deduced from its 400 MHz ^{1}H-NMR spectrum (NOESY) and was confirmed by X-ray diffraction studies of a derivative, as shown below.[8] Hydroboration of **4** with $BH_3{\cdot}Me_2S$ (THF) followed by work-up with $NaBO_3{\cdot}4H_2O$ gave the corresponding diol **6**. Using 0.5 equivalent of $BH_3{\cdot}Me_2S$ and stopping the reaction before completion, monoalcohol **5** could be isolated in 43% yield, together with diol **6** (20-30%). These experiments showed that the kinetic desymmetrization of **4** through hydroboration of its olefinic moieties is not an efficient process ($k_1/k_2 \approx 2$ for the two successive hydroborations) unless a homochiral hydroboration agent is used. This was indeed the case for the hydroboration of **4** with monoisopinocampheylborane ((+)-IpcBH$_2$).[9] Using 1.1 equivalent of (+)-IpcBH$_2$ in THF (-25°C, 22 h) and a work-up with $NaBO_3{\cdot}4H_2O$, the optically active alcohol (+)-**5**[10] was obtained in 59% yield, together with some unreacted **4** and products of decomposition ($(k_1 + k'_1)/(k_2 + k'_2) > 2$ in this case). Because of serious steric hindrance the ketone moieties in **4** and **5** were not reduced with boranes.



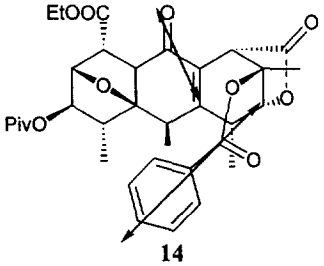
The Mosher's ester[11] **7** obtained through esterification with (S)-(MeO)(CF_3)(C_6H_5)CCOCl (Et_3N, 4-Me_2N-pyridine, CH_2Cl_2, 20°C) showed (400 MHz ^{1}H-NMR) a 78% e.e. for (+)-**5**. According to the Dale's and Mosher's method[12] the absolute configuration of the major ester **7** is that shown as the bridgehead methyl group Me-C(2) is more shielded (δ_H 1.477 ppm) than that of the minor diastereomer (δ_H 1.519 ppm). This assignment was confirmed by single crystal X-ray diffraction (see Figure) of the optically pure ester **8** obtained by esterification of (+)-**5** with (+)-camphor-10-sulfonyl chloride (Et_3N, 4-Me_2N-pyridine, CH_2Cl_2).

Having found a simple way to desymmetrize the meso adduct **4** and having installed the optical activity, we had to explore the possibilities to differentiate the chemistry of the two 7-oxabicyclo[2.2.1]heptane moieties of (+)-**5**. A method has been found as described in Scheme 2. Oxidation of (+)-**5** (PCC, CH_2Cl_2, activated 3 Å molecular sieves, 20°C, 15 h) afforded (+)-**9**.[13] Reduction of (+)-**9** with Na(CN)BH_3 (AcOH/MeOH, 20°C, 4 h) was highly chemo- and stereoselective as only the 3-oxo group was reduced giving the corresponding 3-*endo*-alcohol which underwent fast lactonisation with the *endo* ester function at C(1) providing lactone (-)-**10** in 92% yield.[14] Again steric hindrance makes the 9-oxo group little reactive toward nucleophilic additions. The treatment of (-)-**10** with an excess of $BH_3{\cdot}Me_2S$ in THF (20°C, 6.5 h), followed by work-up with $NaBO_3{\cdot}4H_2O$ (20°C, 15 h), afforded (-)-**12** in 57% yield.[15] It arises form the expected *exo* face hydroboration of the alkene at C(5)-C(6) of (-)-**10**, giving the intermediate **11** which underwent oxa ring opening of its 2,4a-epoxy moiety, a 1,4-elimination induced by the alkaline medium.[16] The 7,10a-epoxy functions of **11** and (-)-**12** were not opened as readily, probably because of the higher strain liberated by the oxanorbornane moiety of **11** bearing the lactone. Alcohol **11** was observed as a secondary product, the proportion of which could reach 15-20% when the time of exposure to the basic conditions ($NaBO_3$) was shortened.

Scheme 2



The Mosher's ester **13** derived from (-)-**12** and (S)-(MeO)(CF_3)(Ph)CCOCl showed a d.e. of 72% and confirmed[12] the absolute configuration shown (δ_H[Me-C(2)]] = 1.48 ppm, 1.415 ppm for the major and minor diastereomer, respectively). Treatment of (-)-**12** with pivaloyl chloride (Et_3N, CH_2Cl_2, 4-Me_2N-pyridine, 20°C, 15 H) and then with $PhCOOSO_2CF_3$[17] provided **14**, the circular dichroism spectrum of which showed the expected exciton-split Cotton effects[18] ($\Delta\varepsilon_{247}$ = +14.7, $\Delta\varepsilon_{213}$ = -5.5, CH_3CN) consistently with the configuration shown for **14** and in which the enone main electric transition ($\pi \rightarrow \pi^*$) moment couples with that of the benzoate, the two chromophores realizing a positive helical arrangement.[19,20]



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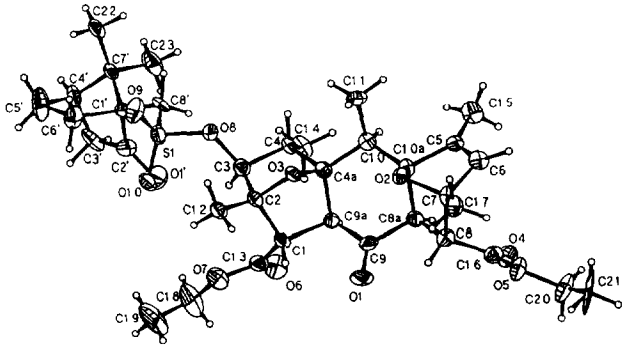

Figure: ORTEP representation of **8**

The work disclosed here sets the stage for a versatile chemistry based on the double Diels-Alder additions of 1,1-bis(3,5-dimethylfur-2-yl)ethane; our preliminary results open a potentially useful and new approach to the asymmetric synthesis of long chain polypropionate fragments.[2,3b,6]

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[5] This concept has been used in our group for the doubly-convergent synthesis of anthracyclinones; see e.g.: Carrupt, P.-A.; Vogel, P. *Tetrahedron Lett.* **1979**, *20*, 4533-4536; Dienes, Z.; Antonsson, T.; Vogel, P. *Ibid.* **1993**, *34*, 1013-1016.

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[8] Data for **4**: m.p. 130-131°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 5.83 (q, ^4J=1.7, HC(3), HC(6)), 4.09 (m, CH_2O), 3.67, 2.99 (2d, ^3J=3.0, HC(1), HC(8), HC(8a), HC(9a)), 2.88 (q, ^3J=7.3, HC(10)), 1.88 (d, ^4J=1.7, MeC(4), MeC(5)), 1.71 (s, MeC(2), MeC(7)), 1.24 (t, ^3J=7.0), 1.10 (d, ^3J=7.3, MeC(10)).

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[10] Data for (+)-**5**: m.p. 55-56°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 5.80 (q, ^4J=1.5, HC(6)), 4.16, 4.08 (2m), 3.70 (d, ^3J=4.3, HC(1)), 3.67 (d, ^3J=3.0, HC(8)), 3.35 (d, ^3J=3.5, HC(3)), 3.29 (dd, ^3J=4.3, ^4J(HC(9a),HC(8a))=0.8, HC(9a)), 2.92 (dd, ^3J=3.0, ^4J=0.8, HC(8a)), 2.55 (q, ^3J=7.3, HC(10)), 2.07 (qd, ^3J=7.6, 3.5, HC(4)), 1.82 (d, ^4J=1.5, MeC(5)), 1.70 (s, MeC(7)), 1.57 (s, MeC(2)), 1.28, 1.24 (2t, ^3J=7.4), 1.25 (d, ^3J=7.6, MeC(4)), 1.44 (d, ^3J=7.3, MeC(10)).

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[13] Data for (+)-**9**: m.p. 166-168°C; IR (KBr): 1752, 1730, 1703 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 5.84 (q, ^4J=1.7), 4.18-4.05 (m), 3.76 (d, ^3J=4.4), 3.68 (d, ^3J=2.8), 3.42 (dq, ^3J=4.4, ^4J=0.9), 2.97 (dq, ^3J=2.8, ^4J=0.9), 2.68 & 2.65 (2q, ^3J=7.0, 7.2), 1.85 (d, ^4J=1.7), 1.72 & 1.58 (2s, 2 Me), 1.27 & 1.25 (2t, ^3J=7.0), 1.27 & 1.20 (2d, ^3J=7.2, 7.0, 2 Me).

[14] Data for (-)-**10**: oil, IR (KBr): 1783, 1718 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 5.83 (q, ^4J=1.7, HC(6)), 4.31 (dd, ^3J=8.2, ^4J=0.9, HC(3)), 4.10 (q, ^3J=7.0, CH_2O), 3.69 (d, ^3J=3.0, HC(8)), 3.52 (dd, ^3J=1.0, ^4J=0.9, HC(1)), 3.10 (dd, ^3J=1.0, ^4J=0.7, HC(9a)), 2.95 (d, ^3J=3.0, ^4J=0.7, HC(8a)), 2.60 (q, ^3J=7.1, HC(10)), 2.38 (qd, ^3J=7.5, 7.4, HC(4)), 1.84 (d, ^4J=1.7, MeC(5)), 1.72 & 1.64 (2s, 2 Me), 1.25 (t, ^3J=7.0, *Me*CH_2), 1.14 (d, ^3J=7.1, MeC(10)), 1.08 (d, ^3J=7.5, MeC(4)).

[15] Data for (-)-**12**: oil, IR (KBr): 3447, 2925, 1785, 1727, 1664, 1618, 1458, 1381, 1341, 1238, 1183, 1058, 966, 891 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 4.20 (m, 2 CH_2), 4.15 (dd, ^3J=2.7, ^4J=1.4, HC(6)), 3.91 (d, ^4J=1.4, HC(8)), 3.40 (d, ^3J=2.6, HC(3)), 3.33 (d, ^3J=4.1, HC(1)), 3.23 (d, ^3J=4.1, HC(9a)), 3.02 (qd, ^3J=7.5, 2.7, HC(5)), 2.75 (q, ^3J=7.4, HC(10)), 1.99 (qd, ^3J=7.4, 2.6, HC(4)), 1.55 & 1.53 (2s, 2 Me), 1.32 (d, ^3J=7.4, MeC(10)), 1.30 (t, ^3J=7.0, Me), 1.29 (d, ^3J=7.5, MeC(5)), 1.17 (d, ^3J=7.5, MeC(4)); ^{13}C-NMR (100.61 MHz, $CDCl_3$) δ_C 195.1 (s, C(9)), 173.2 & 170.5 (2s, C(11), C(12)), 159.5, 124.7, 88.4, 87.3 (4s), 84.8 (d, ^1J(C,H)=157, C(6)), 78.7 (d, ^1J(C,H)=147, C(3)), 72.3 (s, C(7)), 61.4 (t), 54.7, 51.1, 49.0, 45.9, 34.5, 31.8 (6d), 24.1, 16.5, 14.2, 12.59, 12.58, 12.57 (6q).

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[19] All new compounds described in this paper were fully characterized by their spectral data (including COSY and NOESY-2-D-^{1}H-NMR) and their elemental analyses.

[20] Crystallographic data for the structure of **8** have been deposited with the *Cambridge Crystallographic Data Centre*, 12 Union Rd, Cambridge.

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